of claims 28 and 29), that is neither necessitated by Applicant's amendment of the claims nor a submission of an information disclosure statement. See M.P.E.P. §706.07(a).

Rejection of Claims 14-17 Under 35 U.S.C. §102(a)

Claims 14-17 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Ge *et al.* (J. Bacteriology, 1997) ("**Ge I**"). Applicants respectfully traverse the rejection.

The Office Action asserts that Ge I discloses a *B. burgdorferi* FlaA protein. The Office Action further asserts that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art. The Office Action asserts that if the prior art structure is capable of performing the intended use, then it meets the claim.

The authors of Ge I followed up their January 1997 article with an article in July of 1997 (Ge & Charon, Infection Immunity, 65:2992 (1997); "**Ge II**"; of record). The July 1997 article further characterized the FlaA protein disclosed in the January 1997 article (Ge I). Ge II expressly advises against the use of the FlaA protein in diagnosing Lyme disease. Ge II concluded:

> FlaA **is not an immunodominant antigen** in Lyme disease. (second column, heading, p. 2993)(emphasis added)

and

> ...FlaA is a protein unique to spirochetes, our results suggest that it **is not a good candidate** for the serodiagnosis of Lyme disease. (second column, last sentence, p. 2994)(emphasis added).

Ge II could not more clearly express their mistaken belief that FlaA is a suitable antigen to pursue in a test kit or diagnostic test for Lyme disease than in the title of the article: "**FlaA, a Putative Flagellar Outer Sheath Protein, is Not an Immunodominant Antigen Associated**

with Lyme Disease." Therefore, the FlaA protein of Ge I, which was characterized in Ge II, is not a diagnostic reagent because Ge II specifically states that it is not a diagnostic reagent.

The Office Action also asserts that the recitation of a diagnostic reagent is not entitled to any patentable weight because the recitation occurs in the preamble.

Ge I does not teach a diagnostic reagent. Ge I does not disclose that FlaA is a diagnostic reagent and the follow-up article, Ge II, specifically teaches that FlaA is not a diagnostic reagent. "The effect preamble language should be given can be resolved only on review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." *Corning Glass Works v. Sumitomo Electric U.S.A., Inc.*, 9 U.S.P.Q2d 1962, 1966 (Fed. Cir. 1989). "Whether a preamble stating the purpose and context of the invention constitutes a limitation of the claimed process is determined on the facts of each case in light of the overall form of the claim, and the invention as described in the specification and illuminated in the prosecution history." *Applied Materials, Inc. v. Advanced Semiconductor Materials*, 40 U.S.P.Q.2d 1481, 1488 (Fed. Cir. 1996). Additionally, "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention." *Catalina Marketing Int'l Inc. v. Coolsavings.com Inc.*, 67 U.S.P.Q.2d 1781, 1785 (Fed. Cir. 2002).

The instant application and prosecution history clearly reveal that the invention is the surprising discovery, contrary to the teachings of the prior art, that FlaA is indeed a diagnostic reagent. Therefore, because the instant application and prosecution history clearly rely on the preamble, the preamble is properly given patentable weight in this case. Ge I, in view of the

teachings of Ge II, does not teach a FlaA diagnostic reagent. Therefore Ge I cannot anticipate the instant claims.

Rejection of Claims 14, 16, 20, 24, and 26 Under 35 U.S.C. §102(a)

Claims 14, 16, 20, 24, and 26 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Fikrig *et al.* (WO 97 42325) ("**Fikrig I**"). Applicants respectfully traverse the rejection.

The Office Action states that Fikrig teaches a 37 kDa protein and that the Applicants have stated that FlaA is P37. The Office Action further asserts that the claims do not recite amino acid sequences of the claimed protein. Therefore, the Office Action concludes that the claims are anticipated by Fikrig I.

The amino acid sequence of Fikrig I's P37 protein is shown in SEQ ID NO:7 of the reference. This is the same amino acid sequence as disclosed in Fikrig *et al.*, Immunity 6:531 (1997) ("Fikrig II") at Figure 1B. The instant specification makes clear that the claimed FlaA protein "should not be confused with another *B. burgdorferi* 37 kDa protein described in a recent report as P37 kDa protein described in a recent report as P37 (Fikrig E. *et al.*, "*Borrelia burgdorferi P35 and P37 proteins, expressed in vivo, elicit protective immunity.*" Immunity 6:531-539), which is expressed *in vivo* only." See page 18, lines 14-18. One of skill in the art, given the specification, which teaches that the claimed FlaA protein is not the P37 protein disclosed by Fikrig, would recognize that FlaA proteins of the instant invention are a completely different proteins with a different function than that of the P37 protein disclosed by Fikrig I and II. For example, the nucleic acid and amino acid sequences for FlaA (SEQ ID NOs:1 and 2) do not share identity with the Fikrig I nucleic and amino acid sequences (SEQ ID NOs:6 and 7).

Additionally, Feng *et al.* (of record, copy attached for Examiner's convenience) teaches that there are several **different 37 kDa** *B. burgdorferi* proteins. Each of which has a **different** function. Feng teaches the discovery of a *B. burgdorferi* 37 kDa protein named Arp. Feng also recognizes two **other** B. burgdorferi 37 kDa proteins exist:

1. FlaA, an outer sheath protein of the periplasmic flagella; and
2. P37, a lipoprotein that is preferentially expressed in vivo and is described in Fikrig II. See page 4172, Col. 1, second full paragraph.

Therefore, Feng teaches that a total of 3 different 37 kDa *B. burgdorferi* proteins. Feng recognizes that :

1. FlaA and Fikrig II's P37 are two different proteins, with two different functions; and
2. That *B. burgdorferi* gene and gene products should be named based on their function, rather than their molecular weight to avoid confusion. See page 4172, Col. 1, second full paragraph.

Applicants have stated that FlaA has been known as P37. The specification disclosed that FlaA had two names ("the P37 [of the instant invention] can be referred to as FlaA." See page 18, line 10-12). The claims state that the protein claimed is FlaA. Applicants have never stated that FlaA is Fikrig I or II's 37 kDa protein. Confusion may have existed if the claims recited "P37" since there are at least three *B. burgdorferi* proteins with that molecular weight. However, only one *B. burgdorferi* protein has been termed FlaA. FlaA is clearly defined and disclosed in the specification. Therefore, it is clear to one of skill in the art that the claims refer to a *B. burgdorferi* protein that is an outer sheath protein of the periplasmic flagella, *i.e.*, FlaA.

Since Fikrig I teaches a completely different protein than the claimed FlaA protein, Fikrig cannot anticipate the claims. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 14, 16, 20, 24, and 26 Under 35 U.S.C. §102(a)

Claims 14, 16, 20, 24, and 26 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Fikrig *et al.* (1997, Immunity) ("**Fikrig II**"). Applicants respectfully traverse the rejection. Fikrig II discloses the same P37 protein as Fikrig I (compare Fikrig I SEQ ID NOs:6 and 7 to Fikrig II Figure 1B). Therefore, the same arguments presented above for Fikrig I apply to this rejection as well and are incorporated by reference.

The instant specification makes clear that the claimed FlaA protein "should not be confused with another *B. burgdorferi* 37 kDa protein described in a recent report as P37 kDa protein described in a recent report as P37 (Fikrig E. *et al.*, "*Borrelia burgdorferi P35 and P37 proteins, expressed in vivo, elicit protective immunity*." Immunity 6:531-539), which is expressed *in vivo* only." See page 18, lines 14-18. One of skill in the art, given the specification, which teaches that the claimed FlaA protein is not the P37 protein disclosed by Fikrig, would recognize that FlaA proteins of the instant invention are completely different proteins with different function than that of the P37 protein disclosed by Fikrig II. For example, the nucleic acid and amino acid sequences for FlaA (SEQ ID NOs:1 and 2) do not share identity with the Fikrig II's nucleic and amino acid sequences (Fig. 1B).

Additionally, Feng discussed above, teaches that there are several **different 37 kDa** *B. burgdorferi* proteins. Each of which has a **different** function. Feng teaches the discovery of a *B. burgdorferi* 37 kDa protein named Arp. Feng also recognizes that two **other** *B. burgdorferi* 37 kDa proteins exist: FlaA and P37, which is described in Fikrig II. See page 4172, Col. 1, second full paragraph. Feng recognizes that FlaA and Fikrig II's P37 are two different proteins, with two different functions.

Applicants have never stated that FlaA is Fikrig I or II's 37 kDa protein. Confusion may have existed if the claims recited "P37" since there are at least three *B. burgdorferi* proteins with that molecular weight. However, only one *B. burgdorferi* protein has been termed FlaA. Therefore, it is clear to one of skill in the art that the claims refer to a *B. burgdorferi* protein that is an outer sheath protein of the periplasmic flagella, *i.e.*, FlaA.

Since Fikrig II teaches a completely different protein than the claimed FlaA protein Fikrig II cannot anticipate the claims. Applicants respectfully request withdrawal of the rejection.

Rejection of Claim 14 Under 35 U.S.C. §102(b)

Claim 14 stands rejected under 35 U.S.C. §102(b) as allegedly anticipated by Godzicki *et al.*, Hansen *et al.*, Johnson *et al.*, or Gasmann *et al.* Applicants respectfully traverse the rejection.

The Office Action asserts that Grodzicki, Hansen, Gasmann, and Johnson anticipate claim 14. The Office appears to have made an anticipation rejection based on multiple references. Ordinarily, only one reference should be used in making a rejection under 35 U.S.C. §102. However, multiple references can be used when the extra references are used to:

1. Prove the primary reference contains an "enabled disclosure;
2. Explain the meaning of a term used in the primary reference; or
3. Show that a characteristic not disclosed in the reference is inherent. See M.P.E.P. §2131.01.

The Office Action has not cited a primary reference and has not alleged any one of the three conditions above applies to the rejection. Therefore, the anticipatory rejection as it relates to the four cited references as a group is invalid. Applicants will address the rejection as if the claims

The specification teaches that the claimed **FlaA** protein is a 37 kDa protein and that it an outer sheath protein of the periplasmic flagella. See page 3, line 30 through page 4, line 2; page 5, line 8-10. The specification also teaches that the previously known 41 kDa flagellin protein **Fla** corresponds to the **FlaB** core filament proteins of other spirochetes. See page 8, lines 1-2. Ge I teaches that a 41 kDa flagellin protein has been reported in *B. burgdorferi* that is encoded by the ***fla*** gene, which is also known as ***FlaB***. See Ge I, page 552, paragraph spanning Col. 1 and Col. 2. The specification teaches that the **Fla** protein is highly cross-reactive antigen of many spriochetes. See page 7, lines19-22. Therefore the **Fla** protein does not necessarily provide accurate results when used a diagnostic reagent. **Fla** and **FlaA** are clearly different proteins.

Each of the cited references clearly refers to the previously known 41 kDa **Fla** protein, and not the claimed **FlaA** protein, which is 37 kDa.

Grodzicki teaches that early Lyme disease patients have antibodies that react with the 41 kDa flagellar antigen and peptides with weights of 25, 55, 58, or 66 kDa. See page 793, Col. 1, first paragraph. Grodzicki clearly does not teach a **FlaA** protein of 37 kDa that is useful as a diagnostic reagent for early Lyme disease.

Hansen teaches the diagnosis of Lyme disease using a *B. burgdorferi* flagella protein that is 41 kDa. See page 340, col. 1, third full paragraph; Figure 2. Hansen clearly does not teach a **FlaA** protein of 37 kDa that is useful as a diagnostic reagent for early Lyme disease.

Gasmann teaches a 41 kDa flagellar protein of *B. burgdorferi* that is useful as a diagnostic reagent of Lyme disease. See abstract. Gasmann clearly does not teach a **FlaA** protein of 37 kDa that is useful as a diagnostic reagent for early Lyme disease.

Johnson teaches the use of a 41 kDa flagellin (**Fla**) antigen of B. burgdorferi for use in diagnosis of Lyme disease. See page 346, Col. 1, second full paragraph; page 348, Col. 2, last paragraph. Johnson clearly does not teach a **FlaA** protein of 37 kDa that is useful as a diagnostic reagent for early Lyme disease.

Each of the cited references do not teach or suggest a *B. burgdorferi* protein **FlaA** protein that is useful for the early diagnosis of Lyme disease. Instead, each of the references discloses the use of a 41 kDa flagellin protein, which the specification teaches is highly cross reactive with spirochetes other than *B. burgdorferi*. *See*, p. 7, lines 19-22. Therefore, the cited references cannot anticipate the claimed invention.

Applicants respectfully request withdrawal of the rejections.

Rejection of Claims 20-26 Under 35 U.S.C. §103

Claims 20-26 stand rejected under 35 U.S.C. §103 as allegedly obvious over Ge I in view of Fikrig I. Applicants respectfully traverse the rejection.

The Office Action asserts that Ge I teaches a FlaA protein and the claimed invention except for the process steps of making the recombinant FlaA protein. The Office Action asserts that Fikrig I teaches the production of recombinant P37 nucleic acids, transformed host cells, their protein products and fusion proteins. The Office Action state that Fikrig I is not relied upon for its DNA sequences, but rather is relied upon for the teaching of making *B. burgdorferi* recombinantly for the diagnosis of Lyme disease. The Office Action concludes that it would have been obvious to one of skill in the art to use the combination of Ge I and Fikrig I, with a reasonable expectation of success of making a diagnostic reagent for the early detection of Lyme disease.

Claim 20 recites a method for producing a diagnostic reagent for early detection of Lyme disease comprising: providing freshly transformed host cells; constructing a DNA expression vector containing an expressible FlaA encoding DNA sequence; transforming a suitable host cell with said expression vector; plating out said transformed host cells; preparing large scale primary cell cultures from transformed host cells taken from a fresh transformant colony; and inducing FlaA protein expression from said host cells in culture to produce a recombinant FlaA protein. Claims 21-26 are dependant upon claim 20.

Applicants submit that the Office Action has not established a *prima facia* case of obviousness. To establish a *prima facia* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combined reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. See M.P.E.P. §2143.

Initially, the references do not teach all the claim limitations. The cited references do not teach an element of the claims, namely, the references do not teach or suggest a step of preparing large scale primary cell cultures from transformed host cells taken from a fresh transformant colony.

Secondly, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combined reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make

invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). Neither reference, alone or in combination, suggests the production of a FlaA protein including the step of preparing large scale primary cell cultures from transformed host cells taken from a fresh transformant colony.

Finally, there is no reasonable expectation of success. Ge I discusses a FlaA protein; however, Fikrig I does not teach, suggest or even mention a FlaA protein. Ge I does teach or suggest that FlaA could be used as a diagnostic reagent. The specification teaches that not every *B. burgdorferi* protein antigen has serodiagnotic utility. For example, the specification teaches that OspA and OspB have limited serodiagnonsic utility and that other antigens are expressed exclusively in infected animals. See page 2, lines 20-24. Additionally, there is no teaching or suggestion in Ge I or Fikrig I that FlaA can be produced as diagnostic reagent by a method that includes a step of preparing large scale primary cell cultures from transformed host cells taken from a fresh transformant colony.

Furthermore, as discussed above, in the Ge II follow-up article to Ge I, the authors expressly advise against the use of the FlaA protein in diagnosing Lyme disease. Ge II concluded:

> FlaA **is not an immunodominant antigen** in Lyme disease. (second column, heading, p. 2993)(emphasis added)

and

> ...FlaA is a protein unique to spirochetes, our results suggest that it **is not a good candidate** for the serodiagnosis of Lyme disease. (second column, last sentence, p. 2994)(emphasis added).

Ge II clearly teaches away from the use of FlaA as a diagnostic reagent. As such, one of skill in the art, at the time the invention was filed, would have had no reasonable expectation that FlaA could produced in a method comprising the step of preparing large scale primary cell cultures from transformed host cells taken from a fresh transformant colony, such that a useful diagnostic agent is produced.

Since the references do not provide: a suggestion or motivation to modify the references or to combine reference teachings; a reasonable expectation of success; or all the claim limitations, a *prima facia* case of obviousness has not been established. Applicants respectfully request withdrawal of the rejection.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes this would be helpful in expediting prosecution of this application.

Respectfully submitted,

Date: 6/24/02

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